Society of Critical Care Medicine Guidelines on Glycemic Control for Critically Ill Children and Adults 2024

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RATIONALE: Maintaining glycemic control of critically ill patients may impact outcomes such as survival, infection, and neuromuscular recovery, but there is equipoise on the target blood levels, monitoring frequency, and methods.

OBJECTIVES: The purpose was to update the 2012 Society of Critical Care Medicine and American College of Critical Care Medicine (ACCM) guidelines with a new systematic review of the literature and provide actionable guidance for clinicians.

PANEL DESIGN: The total multiprofessional task force of 22, consisting of clinicians and patient/family advocates, and a methodologist applied the processes described in the ACCM guidelines standard operating procedure manual to develop evidence-based recommendations in alignment with the Grading of Recommendations Assessment, Development, and Evaluation Approach (GRADE) methodology. Conflict of interest policies were strictly followed in all phases of the guidelines, including panel selection and voting.

METHODS: We conducted a systematic review for each Population, Intervention, Comparator, and Outcomes question related to glycemic management in critically ill children (≥ 42 wk old adjusted gestational age to 18 yr old) and adults, including triggers for initiation of insulin therapy, route of administration, monitoring frequency, role of an explicit decision support tool for protocol maintenance, and methodology for glucose testing. We identified the best available evidence, statistically summarized the evidence, and then assessed the quality of evidence using the GRADE approach. We used the evidence-to-decision framework to formulate recommendations as strong or weak or as a good practice statement. In addition, "In our practice" statements were included when the available evidence was insufficient to support a recommendation, but the panel felt that describing their practice patterns may be appropriate. Additional topics were identified for future research.

RESULTS: This guideline is an update of the guidelines for the use of an insulin infusion for the management of hyperglycemia in critically ill patients. It is intended for adult and pediatric practitioners to reassess current practices and direct research into areas with inadequate literature. The panel issued seven statements related to glycemic control in unselected adults (two good practice statements, four conditional recommendations, one research statement) and seven statements for pediatric patients (two good practice statements, one strong recommendation, one conditional recommendation, two "In our practice" statements, and one research statement), with additional detail on specific subset populations where available.

CONCLUSIONS: The guidelines panel achieved consensus for adults and children regarding a preference for an insulin infusion for the acute management of hyperglycemia with titration guided by an explicit clinical decision support tool and frequent (≤ 1 hr) monitoring intervals during glycemic instability to minimize hypoglycemia and against targeting intensive glucose levels. These recommendations are intended for consideration within the framework of the patient's existing

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clinical status. Further research is required to evaluate the role of individualized glycemic targets, continuous glucose monitoring systems, explicit decision support tools, and standardized glycemic control metrics.

KEYWORDS: adult; critical illness; decision support; hyperglycemia; insulin; pediatric

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Hyperglycemia is common in critically ill patients and may impact outcomes directly and/or be a marker for underlying increased morbidity or mortality. Controversy regarding the degree of glycemic control needed to achieve optimal critical care patient outcomes has persisted for over 2 decades following a report of reduced mortality among single-center, surgical ICU patients treated with insulin and dextrose to maintain intensive (INT) blood glucose (BG) control, 4.4–6.1 mmol/L (80–110 mg/dL) compared with conventional glucose control (CONV), 10–11.1 mmol/L (180–200 mg/dL) (1) (Unit conversion: 1 mmol/L × 18 = mg/dL). A large follow-up multicenter trial of mixed ICU patients demonstrated slightly higher but significant mortality and hypoglycemia risks with INT (4.5–6 mmol/L, 80–108 mg/dL) compared with CONV (8–10 mmol/L, 144–180 mg/dL) (2). An increased odds for mortality is associated with extremes of glucose but lack agreement on the optimal range for patients with and without diabetes mellitus (DM) (3). Current standards suggest avoidance of dysglycemia (severe hyperglycemia, BG > 10 mmol/L [> 180 mg/dL] or hypoglycemia, < 4.4 mmol/L [< 80 mg/dL]) and use of a protocol and monitoring to minimize the risk of hypoglycemia (4–6). Targeting INT may be acceptable for selected patients if hypoglycemia rate is minimal (5).

Consistent glycemic control is challenging in critically ill patients with unstable hemodynamics and varying medications and nutritional delivery. The significant workload associated with insulin therapy and monitoring must also be considered, along with patient-level impact such as sleep disturbance or discomfort relative to desired outcomes of reduced morbidity and mortality. A key component of any glycemic management program is the effectiveness of the protocol, including consistent utilization, adherence, effective monitoring, and quality assessment. Protocols used in the many randomized clinical trials (RCTs) have been heterogeneous, thus potentially contributing to variable findings. This document does not address all aspects of ICU management of hyperglycemia, DM, transition of insulin routes, nutrition, or the impact and treatment of hypoglycemia, thus other literature sources should be evaluated (5, 6).

METHODOLOGY

Panel Membership and Conflict of Interest Management

Society of Critical Care Medicine (SCCM) appointed two chairs (N.G.B., J.J.) and two vice-chairs (M.S., E.L.H.) (leadership team) who then convened a multiprofessional panel of 15 additional experts in glycemic management in critically ill children and adults plus two patient/family advocates who volunteered to participate when asked by a co-chair (**Supplemental Digital Content 1**, http://links.lww.com/CCM/H476). The total professional panel included six adult intensivists, three endocrinologists, three pediatric intensivists, one cardiac surgeon, two adult pharmacy specialists, one pediatric pharmacy specialist, and three advanced practice providers (adult and pediatric) selected based on their expertise and areas of interest. The Guidelines in Intensive Care Development and Evaluation group appointed a clinician-methodologist (K.H.), for methodological support. SCCM provided logistical and material support. We collected and reviewed financial and intellectual conflicts of interest of each panel member according to the American College of Critical Care Medicine/SCCM Standard Operating Procedures (**Supplemental Digital Content 2**, http://links.lww.com/CCM/H476).

Guideline Scope, Question Development, and Outcome Prioritization

Guideline scope was established by the chairs and vice chairs and approved by the panel. The primary population was identified as unspecified or mixed critically ill patients (i.e., acute illness and treated in a high acuity setting), including subpopulations (e.g., medical, surgical, neurologic, trauma, etc.). The full panel participated in formulating actionable Population, Intervention, Comparator, and Outcomes (PICO) questions related to glycemic management in critically ill children (≥ 42 wk old adjusted gestational age to 18 yr old) and adults (**Supplemental Digital Content 3**, http://links.lww.com/CCM/H476). Neonatal patients

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were excluded due to fundamental differences in physiology, nutrition, and inadequate expertise among panel members. A list of relevant outcomes was defined that each panel member then independently rated for priority based on perceived importance from patients' perspectives. Important outcomes are hospital mortality, ICU mortality, pediatric developmental outcomes, quality of life, seizures, long-term cognitive impairment, and acute kidney injury, among others (**Supplemental Digital Content 4**, http://links.lww.com/CCM/H476). Only the outcomes that were specifically reported in published RCTs were analyzed.

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Systematic Review Process

With assistance from a medical librarian, we performed a systematic review of the literature to identify potentially relevant studies and included those from January 2000 to January 2023 (**Supplemental Digital Content 5**, http://links.lww.com/CCM/H476). A team of reviewers screened all records independently and in duplicate and selected relevant studies. They then extracted data for adults and pediatric ages and each outcome of interest then performed a risk of bias assessment. We synthesized the data by performing meta-analyses using random-effects models and inverse variance weighting (7) or summarized the evidence narratively, depending on data availability (**Supplemental Digital Content 6**, http://links.lww.com/CCM/H476).

Grading of Recommendations, Assessment, Development, and Evaluation Methodology

We assessed certainty in the evidence for each outcome using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) methodology (8) and used GRADEPro GDT to generate evidence profiles for each PICO question (www.gradepro.org). The panel then used the GRADE Evidence-to-Decision framework to generate recommendations, either for or against each intervention, each classified as "Strong" or "Conditional" (**Table 1**). For PICOs lacking adequate evidence to allow us to generate a recommendation, we generated "In our practice" statements, which are unGRADED statements reflecting the general practice of panel experts, or "Good Practice Statements" which are considered equivalent to a strong recommendation (**Supplemental Digital Content 7**, http://links.lww.com/CCM/H476).

TABLE 1.
Grading of Recommendations Assessment, Development, and Evaluation Approach Classification of Recommendation Strengths and Their Implications

Impact	Strong Recommendation "We Recommend…"	Conditional Recommendation "We Suggest…"
Definition	Desirable effects of intervention clearly outweigh undesirable effects, or clearly do not	Trade-offs are less certain, either because of low-quality evidence or because evidence suggests desirable and undesirable effects are closely balanced
Implications for patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not	The majority of individuals in this situation would want the suggested course of action, but many would not
Implications for clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences	Different choices are likely to be appropriate for different patients, and therapy should be tailored to the individual patient's circumstances. Those circumstances may include the patient or family's values and preferences
Implications for policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place

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Final Consensus

Panel members voted on each recommendation and consensus was defined as 80% agreement among at least 75% of voting panel members (**Supplemental Digital Content 8**, http://links.lww.com/CCM/H476). The six PICO questions are listed in **Table 2** and the final recommendations, separated for adults and pediatrics are listed in **Table 3**.

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RECOMMENDATIONS FOR CRITICALLY ILL ADULTS

1. What Glucose Level Should Trigger Initiation of Insulin Therapy for Critically Ill Adults?

Good Practice Statement. Clinicians should initiate glycemic management protocols and procedures to treat persistent hyperglycemia greater than or equal to 10 mmol/L (180 mg/dL) in critically ill adults.

Rationale. We identified no studies that evaluated the optimal BG to "trigger" initiation of insulin infusion therapy in critically ill adult patients separately from the target treatment glucose range. However, the panel considers it to be good practice to manage persistent hyperglycemia (two consecutive BG ≥ 10 mmol/L [180 mg/dL]) with evaluation of glucose intake, additional monitoring, and insulin therapy. The trigger threshold is lower than the treatment goal to avoid prolonged periods above the treatment target range. While hyperglycemia is associated with a stress response and a marker of more severe illness and insulin resistance, it is also associated with harm. Significant hyperglycemia in critically ill patients causes osmotic

TABLE 2.
Summary of Population, Intervention, Comparator, and Outcomes Questions

1) Trigger blood glucose for insulin initiation
In "adult critically ill patients," should we recommend initiating IV insulin therapy at a lower glucose threshold 6.1–10 mmol/L (110–180 mg/dL) or higher glucose threshold > 10 mmol/L (> 180 mg/dL)?
In "pediatric critically ill patients," should we recommend initiating IV insulin therapy at a lower glucose threshold 6.1–10 mmol/L (110–180 mg/dL) or higher glucose threshold > 10 mmol/L (> 180 mg/dL)?
2) Intensive vs. conventional glucose targets
In "adult critically ill patients on insulin therapy," should we recommend a lower blood glucose target 4.4–7.7 mmol/L (80–139 mg/dL) "or" a higher glucose target 7.8–11.1 mmol/L (140–200 mg/dL)?
In "pediatric critically ill patients on insulin therapy," should we recommend a lower blood glucose target 4.4–7.7 mmol/L (80–139 mg/dL) "or" a higher glucose target 7.8–11.1 mmol/L (140–200 mg/dL)?
3) Continuous IV infusion vs. intermittent subcutaneous insulin
"In the acute management of adult critically ill patients for whom insulin therapy is being initiated," should we recommend initiating continuous IV insulin infusion "or" intermittent subcutaneous insulin?
"In the acute management of pediatric critically ill patients for whom insulin therapy is being initiated," should we recommend initiating continuous IV insulin infusion "or" intermittent subcutaneous insulin?
4) Frequency of blood glucose monitoring
"In adult critically ill patients on insulin infusion therapy," should we recommend monitoring of glucose at frequent intervals (≤ 1 hr, continuous or near-continuous) "or" longer intervals (> 1 hr), during the period of glycemic instability?
"In pediatric critically ill patients on insulin infusion therapy," should we recommend monitoring of glucose at frequent intervals (≤ 1 hr, continuous or near-continuous) "or" longer intervals (> 1 hr), during the period of glycemic instability?
5) Use of explicit clinical decision support tool vs. standard care
"In adult critically ill patients on insulin infusion therapy," should we recommend an explicit clinical decision support tool vs. a protocol with no explicit clinical support tool for insulin titration?
"In pediatric critically ill patients on insulin therapy," should we recommend an explicit clinical decision support tool vs. a protocol with no explicit clinical support tool for insulin titration?
6) Glucose monitoring with a meter
"In critically ill patients (adult and pediatric)", can a point of care device be used for blood glucose monitoring or a central laboratory device, using an arterial or venous specimen

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TABLE 3.
Summary of Recommendations

Statement	Type of Statement	Certainty in the Evidence
Adults		
Clinicians should initiate glycemic management protocols and procedures to treat persistent hyperglycemia, ≥ 10 mmol/L (180 mg/dL) in critically ill adults	Good practice statement	NA
Clinicians should use glycemic management protocols and procedures that demonstrate a low risk of hypoglycemia among critically ill adults and should treat hypoglycemia without delay	Good practice statement	NA
Based on available randomized controlled trial data, in critically ill adults, we "suggest against" titrating an insulin infusion to a lower BG target INT: 4.4–7.7 mmol/L (80–139 mg/dL) as compared with a higher BG target range, CONV: 7.8–11.1 mmol/L (140–200 mg/dL) to reduce the risk of hypoglycemia	Conditional recommendation	Moderate
Observational data suggest a potential benefit of personalized glucose targets that more closely match chronic prehospital glycemic control. We recommend high-quality interventional trials of individualized glycemic targets in critically ill adults, stratified by prior glycemic control (such as indicated by glycosylated hemoglobin A1c)	Research statement	NA
We "suggest" using continuous IV insulin infusion rather than intermittent subcutaneous insulin in the acute management of hyperglycemia in critically ill adults	Conditional recommendation	Very low
We "suggest" frequent (≤ 1 hr, continuous or near-continuous) glucose monitoring compared with monitoring at intervals greater than hourly in the management of hyperglycemia in critically ill adults on IV insulin during periods of glycemic instability	Conditional recommendation	Low
We "suggest" use of a protocol that includes explicit decision support tools (tools) over a protocol with no such tools in critically ill adults receiving IV insulin infusions for the management of hyperglycemia	Conditional recommendation	Moderate
Pediatrics		
Clinicians should initiate glycemic management protocols and procedures to treat persistent hyperglycemia, ≥ 10 mmol/L (180 mg/dL) in critically ill children	Good practice statement	NA
Clinicians should use glycemic management protocols and procedures that demonstrate a low risk of hypoglycemia among critically ill children and should treat hypoglycemia without delay	Good practice statement	NA
We "recommend against" INT BG control, 4.4–7.7 mmol/L (80–139 mg/dL) as compared with CONV BG control, 7.8–11.1 mmol/L (140–200 mg/dL) in critically ill children	Strong recommendation	Moderate
We make "no recommendation" regarding the use of continuous IV infusion for insulin therapy over intermittent subcutaneous insulin, in the acute management of hyperglycemia in critically ill pediatric patients in whom insulin therapy is indicated. However, "in our practice," our pediatric-expert panel members use continuous IV infusion over intermittent subcutaneous insulin in critically ill pediatric patients with hyperglycemia	"In our practice" statement	NA
We make "no recommendation" regarding frequent BG monitoring (interval ≤ 1 hr, continuous or near-continuous) or less frequent (> 1 hr) in pediatric critically ill patients on insulin infusion therapy. However, "in our practice," we almost always use frequent (interval ≤ 1 hr) or continuous/near-continuous monitoring systems (if available) in children being treated with insulin infusion therapy	"In our practice" statement	NA
We "suggest" use of explicit decision support tools over no such tools in critically ill pediatric patients receiving IV insulin infusions for the management of hyperglycemia	Conditional recommendation	Very low
We strongly recommend high-quality research on the use of explicit decision support tools for insulin infusion titration in pediatric patients	Research statement	NA

BG = blood glucose, CONV = conventional glucose control, INT = intensive glucose control, NA = not applicable.
Unit conversion: 1 mmol/L × 18 = mg/dL.

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diuresis and is associated with dysfunction of the endothelial glycocalyx, inflammation, and possibly mortality, especially in nondiabetic patients (9–11). The American Diabetes Association (ADA) and American Association of Clinical Endocrinology (AACE) similarly recommend initiation of insulin infusion therapy for critically ill adults with persistent severe hyperglycemia (≥ 10 mmol/L on two occasions [> 180 mg/dL]) (5, 6), although no trials indicate a specific, harmful value. Patients with persistent hyperglycemia may also warrant alteration of fluids, nutrition, or medications causing hyperglycemia. The U.S. Centers for Medicare and Medicaid Services has quality measures for hospital-acquired events to measure and report the rate of adults with one BG greater than or equal to 16.7 mmol/L (300 mg/dL) or multiple BG greater than or equal to 11.1 mmol/L (200 mg/dL) also for severe hypoglycemia (< 2.2 mmol/L [40 mg/dL]) plus criteria for failure to monitor adequately (12, 13).

2. Should Insulin Infusion Therapy Be Titrated to Achieve INT BG Targets, 4.4–7.7 mmol/L (80–139 mg/dL) or CONV, 7.8–11.1 mmol/L (140–200 mg/dL) for Unselected (Mixed) Critically Ill Adults or Any Patient Subgroups?

Good Practice Statement. Clinicians should use glycemic management protocols and procedures that demonstrate a low risk of hypoglycemia among critically ill adults and should treat hypoglycemia without delay.

Recommendation. Based on available RCT data, in critically ill adults, we "suggest against" titrating an insulin infusion to a lower BG target INT: 4.4–7.7 mmol/L (80–139 mg/dL) as compared with a higher BG target range, CONV: 7.8–11.1 mmol/L (140–200 mg/dL) to reduce the risk of hypoglycemia (Conditional recommendation; moderate certainty of evidence).

Comments.

- Analysis of data from neurologic or cardiac surgery ICUs yielded comparable findings and these patients should be managed like unselected patients.
- For other specific subsets of critically ill patients (e.g., cardiac, medical, surgical, trauma, etc.) data were inadequate to perform subgroup analyses and thus patients should be managed like unselected patients.
- For the subset of patients with preexisting DM or preadmission hyperglycemia, there is insufficient evidence from RCTs to make a recommendation regarding personalized targets for glycemic control.

Research Statement. Observational data suggest a potential benefit of personalized glucose targets that more closely match chronic prehospital glycemic control. We recommend high-quality interventional trials of individualized glycemic targets in critically ill adults, stratified by prior glycemic control (such as indicated by glycosylated hemoglobin A1c [HbA_1C]).

Rationale.

Evidence summary. Forty-four RCTs compared insulin infusion targets of INT to CONV among mixed populations of ICU patients. There was no impact on hospital mortality (23 RCTs [1, 14–35]; relative risk [RR], 0.91; 95% CI, 0.8–1.02; moderate certainty) or ICU mortality (18 RCTs [1, 2, 14–16, 18, 20–24, 27–29, 36–39]; RR, 0.97; 95% CI, 0.91–1.03; high certainty). Targeting INT was associated with lower ICU length of stay (LOS, 25 studies [1, 2, 14–16, 18–20, 23–29, 31–35, 38, 40–43]; mean difference [MD], –0.48; 95% CI, –0.82 to –0.14; low certainty), reduced infection risk (24 studies [1, 2, 14, 16, 18–20, 22, 24–27, 29–31, 37, 38, 40, 42, 44–48]; RR, 0.79; 95% CI, 0.68–0.91; moderate certainty), and increased frequency of severe hypoglycemia (< 2.2 mmol/L) (29 RCTs [1, 2, 14–28, 35–38, 40–43, 45–47, 49]; RR, 3.75; 95% CI, 2.38–5.9; high certainty). Although INT improved neurologic outcomes in six studies (26, 27, 31, 45, 50, 51) and reduced critical illness polyneuropathy in two (1, 52), all had serious risk of bias (SDC 9-2, http://links.lww.com/CCM/H476).

Two subset groups had adequate data for meta-analysis. Among neurologic ICU patients, INT increased severe hypoglycemia (six RCTs [26, 27, 38, 46, 50, 51]; RR, 2.17; 95% CI, 0.88–5.32; high certainty) but had no effect on other clinically important outcomes (SDC 9-2, http://links.lww.com/CCM/H476). In cardiac surgery patients, INT reduced ICU mortality (two RCTs [28, 52]; RR, 0.43; 95% CI, 0.21–0.87), but this finding was extensively driven by one RCT (52). Severe hypoglycemia was however increased by INT targets (five RCTs [28, 35, 42, 47, 52]; RR, 4.0; 95% CI, 1.38–11.61; high certainty). There were no effects on other clinically important outcomes (SDC 9-2, http://links.lww.com/CCM/H476).

For other specific patient subsets (medical or surgical ICU, trauma, cardiac, etc.), data were inadequate to perform subgroup analyses. INT had a potential signal for increased mortality among patients with prior DM (six RCTs [1, 2, 15, 16, 18, 22]; RR, 1.12; 95% CI, 0.97–1.29), but not in those without DM (five RCTs [1, 2, 15, 16, 22]; RR, 0.97; 95% CI, 0.79–1.18);

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however, there was low certainty in the evidence (SDC 9-2, http://links.lww.com/CCM/H476).

Evidence to recommendation. : The panel feels that glycemic control is still a relevant component of patient care but suggested against lower targets to maximize safety rather than making a statement in favor of a higher target for all populations based upon the outcomes in existing literature. The tight glucose control without early parenteral nutrition (TGC-Fast) trial (9230 patients) comparing INT, 4.4–6.1 mmol/L (80–110 mg/dL) vs. a higher target than used in this guideline, 10–11.9 mmol/L (180–215 mg/dL) was published after our last literature search (53). There was no difference in time to discharge alive from ICU or 90-day mortality between groups although the high target group had less frequent use of insulin infusions. In that trial, negative outcomes such as hypoglycemia events were minimized with a computerized protocol and careful monitoring procedures. As a result, either target may be acceptable when safety is demonstrated.

In our analysis, the risk of hypoglycemia in most trials was large and consistent in all populations with INT targets, with potential for acute and long-term potential negative impacts including the associated higher mortality reported in observational datasets (54–57), Our meta-analysis of RCT data did not illustrate a higher mortality risk with hypoglycemia (SDC 9-2, http://links.lww.com/CCM/H476). A validated insulin protocol with documented low hypoglycemia rates is essential and was a significant component of the TGC-Fast trial (53) but has not been a consistent feature of included studies. On the basis of a high risk of severe hypoglycemia in most RCTs and small potential benefits of INT, the panel suggests against INT targets for most adult ICU patients, including subsets of cardiac surgery and neuro-ICU. Nonetheless, the panel judged that INT would probably not impact health equity and would probably be feasible and acceptable to stakeholders. Further they agreed that lower targets, 6.1–7.8 mmol/L (110–140 mg/dL) may be acceptable for patients in select centers where the risk of hypoglycemia is documented to be negligible (SDC 9-2*C*, http://links.lww.com/CCM/H476).

Together, this statement and the preceding good practice statement endorse the importance of treating hyperglycemia, BG greater than or equal to 10 mmol/L (180 mg/dL) triggering active management with insulin infusion, while tolerating a higher BG target range of 7.8–11.1 mmol/L (140–200 mg/dL) among patients who have been started on insulin infusion. The optimal upper limit for a glycemic target with insulin infusion is not well defined with current literature.

Subsets of cardiac surgery and neurologic ICU patients similarly did not benefit from INT targets in RCTs for clinically important outcomes. Cardiac surgery patients comprised more than 45% of patients in the TGC-Fast trial but subset analysis similarly showed no difference in outcomes with INT vs. their high target (53).

The limited subset of cardiac surgery patients without DM on INT had fewer complications (42, 58, 59). Existing RCTs do not provide adequate prospective data to guide glycemic targets for patients with and without preexisting DM, despite observational data suggesting a potential difference in outcome with a glucose target matched to prior glycemic control (60). As such, the panel does not provide a glycemic target recommendation based on preexisting DM. A consensus statement for reducing sternal wound infection suggests targeting less than 10 mmol/L (180 mg/dL) (61) and insulin treatment if BG greater than 8.8–10 mmol/L (158–180 mg/dL) (62).

Research considerations. Observational data have generated hypotheses for future RCTs, especially around individualized targets. A lower target in non-DM patients has been associated with benefit and higher mean BG levels are associated with greater mortality (3, 9, 63–67). This contrasts with the failure to show a benefit of INT in TGC-Fast, despite 80% of patients having no history of DM (53). Patients with DM and high admission HbA_1C may have less risk from hyperglycemia (3) but greater mortality with relative hypoglycemia (66, 68, 69). A glycemic ratio of 80–90% is a proposed target (ratio of mean ICU BG/chronic estimated BG) but requires prospective trials using individualized targets with low hypoglycemia rates that achieve adequate time in each target range (70, 71) (**Table 4**). Additional research on the financial impact of glycemic control is also needed, based on the reduced costs associated with INT in cardiac surgery patients (60, 72).

3. In the Acute Management of Hyperglycemia in Adult Critically Ill Patients for Whom Insulin Therapy Is Being Initiated, Should Continuous IV Insulin Infusion or Intermittent Subcutaneous Insulin Be Initiated?

Recommendation. We "suggest" using continuous IV insulin infusion rather than intermittent subcutaneous

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TABLE 4.
Future Research Topics for Glycemic Control of Critically Ill Patients

Research Priority Topic	Details
Impact of individualized glycemic targets based on chronic glycemic control overall and in subset populations	Individualized glycemic control stratified by: Patient population: cardiac, cardiac surgery, medical, neurologic, surgical/ trauma, vascular surgery, etc. No DM Well-controlled DM chronic glucose (e.g., $HbA_1C < 7\%$) Poorly controlled DM chronic glucose (e.g., $HbA_1C \geq 7\%$) Baseline higher vs. lower levels of inflammatory markers
Evaluate hospitalization costs relative to outcome for intensive glucose control vs. conventional glucose control ranges	
IV vs. subcutaneous insulin in critically ill patients	Outcome benefit of IV compared with subcutaneous insulin both in unstable and stable patient populations
CGM systems	Impact of CGM on hypoglycemia, relative hypoglycemia frequency and workload Impact of insulin infusion therapy with closed loop titration and CGM Impact of CGM on safety of normoglycemic glucose targets Accuracy and consistency of new technology in glycemic monitoring (e.g., wearable sensors, intravascular glucose monitors, etc.)
Explicit decision support tools for glycemic control in ICU	Safety and effectiveness of an insulin therapy protocol that meets optimal clinical decision support criteria as outlined in Table 5 Report reproducible protocol in detail Report adherence and complication rates Demonstrate achievement of adequate time in range for each glucose target Determination of which elements are critical to the optimal design of explicit decision support tools for glycemic management and how they impact patient outcomes, particularly with new technology Quantify cost and utility of explicit decision support tools for glycemic management
Defining standardized glycemic control metrics	Define standardized metrics for hypoglycemia and relative hypoglycemia frequency and define appropriate limits for specific patients and populations Define standardized metrics for other variables such as glycemic variability, time in range, or other measures of glucose control
Evaluate the challenges/benefits of incorporating glycemic management tools into the electronic health record	

CGM = continuous glucose monitoring, DM = diabetes mellitus, HbA_1C = glycosylated hemoglobin A1c.

insulin in the acute management of hyperglycemia in critically ill adults (conditional recommendation, very low certainty evidence).

Rationale.

Evidence summary. Six studies (two RCT [73, 74], four observational studies [75, 76]) reported outcomes of IV insulin infusion vs. intermittent subcutaneous insulin in critically ill adults with hyperglycemia (**SDC 9-3**, http://links.lww.com/CCM/H476). There was no effect of IV insulin infusion on mortality (one RCT [73]; two observational studies [75, 76]), ICU LOS (two RCTs [75, 76]), hospital LOS (two RCTs [75, 76]),

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TABLE 5.
Minimum Requirement for Explicit Decision Support Tools for Glycemic Management

Criterion	Description
Explicit recommendations	Bedside clinician knows exactly what to do with each BG level
Reproducible actions	Same patient situation would be treated the same way
Two or more patient-specific input variables	Examples of inputs include: BG level, change or rate of change in BG level, hypoglycemia episodes, nutritional intake, etc.
Two or more output variables	Examples of outputs include: change in insulin rate, timing of next BG, etc.
Open-loop system	Allows for the clinician to agree or disagree with the recommendation

BG = blood glucose.

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and total infections (one RCT [73]; for all outcomes: low certainty for RCTs; very low certainty for the observational studies). Insulin infusion achieved the target glycemic range more often (one RCT [74]; moderate certainty; three observational studies [76–78]; very low certainty). However, there was an increase in the number of hypoglycemic episodes with IV therapy (two RCTs [73, 74]; moderate certainty) not seen in two of four observational studies (76, 77) (very low certainty).

Evidence to recommendation. Desirable effects of insulin infusion may include better glycemic control, although this finding is limited to RCTs with small sample sizes leading to high imprecision, and there were no benefits on clinical outcomes (e.g., infection) (SDC 9-3*A*, http://links.lww.com/CCM/H476). The panel judged the desirable effects of infusion as small and overall certainty in the evidence low to very low (SDC 9-3*B*, http://links.lww.com/CCM/H476). Undesirable effects of infusion include more frequent monitoring, higher nursing workload and more frequent hypoglycemic episodes and were judged by the panel as undesirable effects of moderate importance. Nighttime awakening for intermittent dosing was undesirable by patient/family advocates on the panel with a preference for reliable vascular access. A comparable daily dose of insulin delivered via the IV vs. subcutaneous route, in theory, could produce similar glycemic control. However, variables of inconsistent absorption with concurrent vasopressors, poor perfusion, and significant edema make subcutaneous dosing less desirable for critically ill patients (4, 79). Nighttime awakening for monitoring is of comparable concern. The difference in resource requirements, cost effectiveness, and workload are likely to be negligible between the two routes. On balance, the evidence does not seem to favor either the intervention or the comparison. The panel deemed insulin infusion to be feasible to implement and acceptable, with some suggesting that it may be less invasive and more comfortable for patients compared with subcutaneous insulin administration. The panel emphasized the need for more high-quality RCTs to determine the effects of the route of insulin administration on patient-important outcomes and separate evaluation for acutely critically ill patients vs. those who are in a recovery phase of critical illness (Table 4).

4. In Adult Critically Ill Patients on Insulin Infusion Therapy, Should BG Be Monitored Frequently (Interval ≤ 1 hr, Continuous or Near-Continuous) or Less Frequently (Interval > 1 hr) During Periods of Glycemic Instability?

Recommendation. We "suggest" frequent (≤ 1 hr, continuous or near-continuous) glucose monitoring compared with monitoring at intervals greater than hourly in the management of hyperglycemia in critically ill adults on IV insulin during periods of glycemic instability (conditional recommendation; low certainty evidence).

Rationale.

Evidence summary. Six RCTs (80–85) evaluated this outcome and showed that more frequent monitoring was associated with reduced frequency of hypoglycemia (variably defined as < 2.2 to < 4.0 mmol/L [40–70 mg/dL]; five RCTs [80–84]; moderate certainty), lower time in hyperglycemic ranges (three RCTs [80, 82, 83]; low certainty), and possibly reduced glycemic variability (assessed with coefficient of variation; three

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RCTs [82–84]; moderate certainty; **SDC 9-4**, http://links.lww.com/CCM/H476). There was no impact on more significant outcomes including hospital mortality (four RCTs [80–83]; low certainty), ICU mortality (four RCTs [80, 81, 83, 84]; very low certainty), need for renal replacement therapy (two RCTs [82, 83]; low certainty), or new infections in the ICU (two RCTs [83, 85]; moderate certainty).

Evidence to recommendations. Desirable effects of more frequent glucose monitoring include improved glycemic control and reduced hypoglycemia rates plus earlier detection (SDC 9-4*A*, http://links.lww.com/CCM/H476). Undesirable effects include a greater nursing workload and added cognitive load, which may distract from other patient-care activities. Frequent fingerstick testing is potentially painful and harmful compared with an indwelling vascular access source. The frequency of glucose monitoring that is acceptable for clinically stable patients (consistent nutritional intake, medications and doses, hemodynamics, etc.) may be longer, but risks undetected hypoglycemia. The ADA and AACE suggest monitoring every 30 minutes to 2 hours during insulin infusions (5, 6).

Subcutaneous continuous glucose monitoring (CGM) has been employed with observational evidence suggesting its potential utility to reduce the frequency of point of care (POC) glucose testing although some concurrent POC verification is still advised (see PICO-6). Further, CGM assessment at least hourly may reduce workload if used for insulin titration (19 min lower/24 hr) (one RCT [80]; moderate certainty). Intravascular CGM is only available in limited locations and generally only in research settings.

Overall, the panel deemed the balance of effects to favor more frequent (≤ 1 hr) glucose monitoring for improved safety in critically ill patients (SDC 9-4*C*, http://links.lww.com/CCM/H476).

Special considerations. Glucose measurement accuracy is influenced by operator skill, sampling site, assay device, and frequency as previously reviewed (4, 86). Subcutaneous and capillary measurement sites may lag before registering a change in glucose may be impacted by tissue edema or reduced perfusion with concurrent vasopressors and device calibration is needed to maintain accuracy. Additionally, routine use of CGM for hospitalized patients will require regulatory approval, substantial training, use of protocols, and a system for integration of results into the electronic health record (EHR). Research is needed using established metrics and clinical variables as described in a recent literature (87–89) (Table 4).

5. In Adult Critically Ill Patients on Insulin Infusion Therapy, Should a Protocol That Includes Explicit Decision Support Tools Be Used Compared With Conventional Protocols for the Management of Hyperglycemia?

Recommendation. We "suggest" use of a protocol that includes explicit decision support tools (tools) over a protocol with no such tools in critically ill adults receiving IV insulin infusions for the management of hyperglycemia (conditional recommendation, moderate certainty evidence).

Rationale.

Evidence summary. We defined explicit clinical decision support tools as those that provide all the elements listed in **Table 5** preferably with computerized support and interoperability of the tool with the EHR. We identified 13 RCTs (85, 90–101) (including five [85, 98–101] among cardiac surgery patients) that compared tools to conventional glycemic management protocols without tools (**SDC 9-5**, http://links.lww.com/CCM/H476). The addition of tools was associated with reduced episodes of moderate hypoglycemia, less than 3.3 mmol/L (60 mg/dL) (five RCTs [94–97, 101]; RR, 0.74; 95% CI, 0.57–0.98; moderate certainty), and more time within target range (MD, 14%; 95% CI, 8.85–19.06; 10 RCTs [85, 91, 92, 94–99]; moderate certainty). The use of tools had no effect on critical patient outcomes including hospital mortality or ICU LOS (moderate certainty), ICU mortality or quality of life at 90 days (low certainty), or other important clinical outcomes, although certainty in these outcomes was downgraded due to inconsistency and imprecision. These findings were consistent across the five RCTs (85, 98–101) evaluating cardiac surgery patients (SDC 9-5*B*, http://links.lww.com/CCM/H476).

Evidence to recommendation. Desirable effects of explicit decision support tools include improved glycemic control, reduced rates of moderate hypoglycemia (< 3.3 mmol/L [60 mg/dL]), and potential increased nursing satisfaction, with low to moderate certainty in the evidence. The panel acknowledged that small sample size, few RCTs, and low baseline mortality rates in included studies may affect the ability to see a

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difference in critical outcomes. Most of these protocols are computerized, thus the cost of the intervention, including monetary, intellectual, training, workload, and software maintenance are moderate, but acknowledge that no studies evaluate cost outcomes. Resource limitations may impact utilization at some sites. Overall, the panel deemed the positive effects probably favor explicit decision support tools over conventional protocols, with low to moderate certainty of evidence. Protocols with explicit decision support have been associated with lower rates of hypoglycemia, even with INT goals (53, 102, 103). The panel does not support any commercial or published explicit decision support tool with the caveat that it should meet the criteria and apply appropriate limits on dosing (Table 5). The panel agreed that institutions must routinely monitor and validate tool outcomes and adherence (SDC 9-5*C*, http://links.lww.com/CCM/H476).

Special considerations. Inputs and outputs for various explicit decision support tools are heterogeneous, making comparisons of differences in clinical trials difficult. It is also difficult to discern which inputs and outputs are the most important and most likely to affect clinical outcomes (mortality, LOS, etc.). The conventional protocol comparators may include some important elements (Table 5) that could mask some important and critical differences in outcomes. Incorporating the tool into the EHR is feasible and likely important (103). Additional research is warranted (Table 4).

RECOMMENDATIONS FOR CRITICALLY ILL CHILDREN

Pediatric patients warrant considerations that are different from adults due to differences in disease states, comorbidities, IV access, and potential outcome. A subgroup of pediatric critical care specialists (E.L.H., M.S.D.A., E.A.F., S.Y.I., V.S.) and a pediatric endocrinologist (M.S.D.A.) engaged with the entire panel but focused specifically on the pediatric statements. The population considered pediatric as age greater than or equal to 42 week adjusted gestational age to 18 years. Neonates and newborns were not included due to fundamental differences in physiology, glucose management, and nutritional requirements when compared with a newborn greater than 2 weeks with a critical illness requiring PICU. Similar to the adult sections, the focus is on the acute period of critical illness with hemodynamic instability, altered perfusion, and unstable nutritional intake.

1. What Glucose Level Should Trigger Initiation of an Insulin Infusion for a Mixed Population of Critically Ill Children

Good Practice Statement. Clinicians should initiate glycemic management protocols and procedures to treat persistent hyperglycemia, greater than or equal to 10 mmol/L (180 mg/dL) in critically ill children.

Rationale. We identified no studies that evaluated the optimal BG to trigger the initiation of insulin therapy in critically ill pediatric patients separately from target BG range. However, the panel considers it to be good practice to treat persistent hyperglycemia, generally defined as two serial BG concentrations greater than or equal to 10 mmol/L (180 mg/dL), which is also the renal threshold for glucosuria (104). While hyperglycemia is attributable to a stress response, it is also a reliable indicator of severity of illness and a prognostic biomarker for poor outcome in critically ill children (without DM), although it remains unproven that the associated poor outcomes are causally related to hyperglycemia. Initial maneuvers as BG levels rise toward 10 mmol/L (180 mg/dL) may be to decrease the glucose infusion rate to generally accepted age-based targets (105) and to remove pharmacologic agents that impair beta cell function or induce insulin resistance, if possible. However, once those strategies have been implemented and hyperglycemia persists, insulin therapy should be initiated with assiduous monitoring to avoid or rapidly identify hypoglycemia.

2. Should Insulin Therapy Be Titrated to Achieve INT BG, 4.4–7.7 mmol/L (80–139 mg/dL) or CONV, 7.8–11.1 mmol/L (140–200 mg/dL) for Unselected (Mixed) Critically Ill Children?

Good Practice Statement. Clinicians should use glycemic management protocols and procedures that demonstrate a low risk of hypoglycemia among critically ill children and should treat hypoglycemia without delay.

Recommendation. We "recommend against" INT BG control, 4.4–7.7 mmol/L (80–139 mg/dL) as compared with CONV BG control, 7.8–11.1 mmol/L

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(140–200 mg/dL) in critically ill children (defined by the pediatric panel as ≥ 42 wk adjusted gestational age) (strong recommendation, moderate certainty evidence).

Rationale.

Evidence summary. Five RCTs reported outcomes of INT vs. CONV BG control in critically ill children in three cohorts of medical-surgical (106–108) and three cohorts of cardiac surgery patients (107, 109–111) (**SDC 10-2**, http://links.lww.com/CCM/H476). Among medical-surgical pediatric patients, INT had no effect on mortality or new infections (two RCTs [106, 108]; low certainty for both outcomes; SDC 10-2, http://links.lww.com/CCM/H476) but was associated with shorter ICU LOS (two RCTs [106, 107]; MD, –1.1; 95% CI, –2.09 to –0.1; moderate certainty), and significantly more severe hypoglycemia events (three RCTs [106–108]; RR, 2.99; 95% CI, 1.91–4.67; high certainty). There were no differences in neurocognitive outcomes at 1-year follow-up (two RCTs [106, 112, 113]), although there was more improvement in quality-of-life measures and higher health status as assessed by the Health Utilities Index in the CONV group (106, 107, 114).

Analysis was done on a single subset. Among pediatric cardiac surgery patients on INT, there was no effect on mortality (two RCTs [109, 115]; RR, 0.84; 95% CI, 0.27–2.59; high certainty), ICU LOS (three RCTs [107, 109, 115]; MD, –0.05; 95% CI, –0.37 to 0.28; moderate certainty), or new infections (one RCT [109]; RR, 1.0; 95% CI, 0.58–1.74; moderate certainty). There were significantly more patients with severe hypoglycemia events (three RCTs [107, 109, 115]; RR, 4.93; 95% CI, 2.15–11.3; high certainty). In this subset, there were no differences in neurocognitive outcomes based on BG targets at 1- and 3-year follow-up (109, 116, 117). While RCT data were prioritized for this guideline, observational data suggest poorer cognitive performance among children with moderate or severe hypoglycemia events, lending additional importance to hypoglycemia avoidance (106, 109, 116, 118).

Evidence to recommendation. The panel deemed the desirable effects of the INT targets to be trivial based on current RCT evidence. The panel judged the undesirable effects of INT, namely risk of severe hypoglycemia, to be moderate and considered that such events may lead to long-term developmental and neurocognitive problems, although evidence for the latter is limited. Overall certainty in the evidence was moderate. On balance, the panel agreed that while existing evidence favors CONV BG targets, they were more clearly against an INT target. One study reported lower 12-month costs with INT, but the panel deemed certainty in this evidence to be very low due to limited generalizability (107). However, the panel deemed that INT targets probably have no impact on health equity and would be feasible and acceptable to key stakeholders. Nonetheless, based on existing RCT evidence, the panel recommends against intensive BG control in pediatric general medical-surgical and cardiac surgery patients.

Special consideration. Post hoc analysis of independent subpopulations of pediatric medical-surgical ICU (noncardiac surgery) and burn patients found that the subsets with hyperinflammation had a lower mortality associated with INT than those with CONV BG targets (SDC 10-2*C*, http://links.lww.com/CCM/H476). Future prospective trials on patients with elevated inflammatory biomarkers are needed to assess for a difference in outcome with INT vs. CONV targets (119).

3. In the Acute Management of Hyperglycemia in Pediatric Critically Ill Patients for Whom Insulin Therapy Is Being Initiated, Should Continuous IV Insulin Infusions or Intermittent Subcutaneous Insulin Be Initiated?

"In Our Practice" Statement. We make "no recommendation" regarding the use of continuous IV infusion for insulin therapy over intermittent subcutaneous insulin, in the acute management of hyperglycemia in critically ill pediatric patients in whom insulin therapy is indicated. However, "in our practice," our pediatric-expert panel members use continuous IV infusion over intermittent subcutaneous insulin in critically ill pediatric patients with hyperglycemia.

Rationale. There are no comparative data on the use of continuous IV vs. intermittent subcutaneous insulin administration for PICU patients on insulin. However, in our practice, pediatric-expert panel members exclusively use continuous IV insulin infusion to treat hyperglycemia in critically ill children. The more reliable delivery and ease of titration of continuous IV insulin make it preferable to subcutaneous administration with its potentially inconsistent absorption or prolonged effects. Possible undesirable effects of

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continuous insulin infusion include the need for vascular access (occasionally central) and a reliable and consistent caloric source. Patient and family partners on the panel identified both the need for central vascular access (for insulin infusion) and multiple injections (with intermittent subcutaneous injections) as potentially undesirable. They also identified frequent interruptions in sleep or lack of continuity by providers as important factors to consider in the choice of insulin delivery but felt that either route is acceptable if these concerns are mitigated. The difference in resource requirements, cost effectiveness, and workload are likely to be negligible between the two routes. On balance, the panel agreed that avoiding repeated subcutaneous injections in pediatric patients would be valued by both patients and their caregivers.

4. In Pediatric Critically Ill Patients on Insulin Infusion Therapy, Should BG Be Monitored at Frequent Intervals (Interval ≤ 1 hr, Continuous or Near-Continuous) or Less Frequently (> 1 hr) During the Period of Glycemic Instability?

"In Our Practice" Statement. We make "no recommendation" regarding frequent BG monitoring (interval ≤ 1 hr, continuous or near-continuous) or less frequent (> 1 hr) in pediatric critically ill patients on insulin infusion therapy. However, "in our practice," we almost always use frequent (interval ≤ 1 hr) or continuous/near-continuous monitoring systems (if available) in children being treated with insulin infusion therapy.

Rationale. There are no RCTs or observational studies of children treated with insulin infusion that compare frequency of BG monitoring and its relationship to outcomes, nor is there suitable indirect evidence to substantiate a formal recommendation. However, it is well understood that the biggest risk of insulin therapy in critically ill children is unrecognized hypoglycemia. Therefore, more frequent or continuous BG monitoring reduces this risk. The frequency of BG monitoring during an insulin infusion is critical for early detection of hypoglycemia and to minimize glucose variability related to inconsistent nutrition, concurrent medications, fluids, and other clinical changes. Despite relatively frequent monitoring (INT median 17.4 measures per day [interquartile range (IQR), 13.9–10.6] vs. CONV median 7 [IQR, 5.5–11.5]), hypoglycemia was still more frequent, and often detected by continuous subcutaneous monitoring in one RCT (106). Unfortunately, there are limited data on the optimal frequency of BG monitoring and the impact on patient outcome for PICU patients on insulin infusions. The two most robust trials in critically ill children used adjunctive subcutaneous CGM monitoring for safety reasons (106, 109, 120). For comparison, in "adult" data, more frequent BG monitoring was associated with reduced frequency of hypoglycemia, < 2.2 to < 4.0 mmol/L (40–72 mg/dL) variably defined by the author (five RCTs [95–97, 101, 121]; moderate certainty), less time in hyperglycemic range (three RCTs; low certainty), and possibly reduced glycemic variability (three RCTs; moderate certainty). For these reasons, our panel members always employ frequent or continuous/near-continuous BG monitoring in pediatric patients on an insulin infusion. However, our pediatric-expert panel members will reduce frequency of BG monitoring if the patient demonstrates four BG values at goal with clinical stability and no change in insulin infusion, nutrition, or medications. The panel recognizes that more frequent BG monitoring may pose a workload burden (122), which may detract from other patient care activities. However, the common practice when employing continuous insulin infusion treatment in critically ill children is to use more frequent BG checks paired with an explicit insulin titration protocol that reacts and adjusts BG frequency to minimize hypoglycemia.

5. In Pediatric Critically Ill Patients on Insulin Infusion Therapy, Should an Explicit Decision Support Tool Be Used Compared With Conventional Care for the Management of Glycemia?

Recommendation. We "suggest" use of explicit decision support tools over no such tools in critically ill pediatric patients receiving IV insulin infusions for the management of hyperglycemia (conditional recommendation; very low certainty evidence).

Research Statement. We strongly recommend high-quality research on the use of explicit decision support tools for insulin infusion titration in pediatric patients.

Rationale.

Evidence summary. One small observational study (123) compared a computerized algorithm (eProtocol insulin) vs. the Yale Insulin Infusion Protocol in PICU patients on insulin therapy and reported higher

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percentage of BG values in the target range with the computerized algorithm, but no difference in mortality, glycemic variability, or rates of hypoglycemia (very low certainty for all outcomes; **SDC 10-5**, http://links.lww.com/CCM/H476).

Evidence to recommendation. The panel deemed the certainty in the evidence to be very low, impeding the ability to draw conclusions around the clinical benefits of clinical decision support tools to guide insulin titration in critically ill children. However, the panel notes that the most robust RCT to date in critically ill children used an explicit decision support tool in both arms of the intervention (106). The panel expressed concerns around the increased workload, changes in cognitive burden, and training time around the complexity of the intervention and considered that the cost of computerized tools could be prohibitive in widespread implementation (SDC 10-5*B*, http://links.lww.com/CCM/H476). Overall, the processes to manage hyperglycemia with an insulin infusion are similar between pediatrics and adults. On the basis of data from the adult ICU literature, in which use of clinical decision support tools reduced frequency of hypoglycemia (five RCTs [95–97, 101, 121]; moderate certainty) and increased time within target BG range (10 RCTs [85, 91, 92, 95–99, 121]; moderate certainty), the panel suggests the use of such tools where available and feasible (SDC 9-5*C*, http://links.lww.com/CCM/H476). The key elements of an explicit decision support tool are listed in Table 5 and are discussed further in the adult section. The panel agreed that high-quality interventional trials are warranted on specific tools relative to implementation, feasibility, and outcomes among critically ill children (Table 4).

ADULT AND PEDIATRIC GLUCOSE MONITORING DEVICES

In Critically Ill Patients (Adult and Pediatric), Can a POC Device Be Used for BG Monitoring As Compared With Central Laboratory Blood-Plasma Device or Blood Gas Analyzer Using an Arterial or Venous Specimen?

Recommendation. The panel is unable to provide a specific statement due to inconsistent methodologies and reporting among comparative studies, but we recognize the need for timely results in a clinical setting.

Rationale. POC glucose meter use in the ICU setting is ubiquitous due to their ability to provide rapid results while maintaining ease of use and ready availability. Many different devices for POC testing have been evaluated and compared with a similarly large number of potential gold standard laboratory devices in central or satellite locations. The quality of any result is highly dependent on potential for error. Preanalytical variables, common in the ICU, fall into three core groupings: the user interface—including the user skills, device-specific, and technique used for specimen collection; patient/therapy factors—such as interfering medication or endogenous substances; and physiologic, reflecting glucose metabolism, capillary-to-plasma glucose gradients, insulin kinetics, and more. Further inaccuracy may result from slow glucose equilibration during hypotension or shock (124), with vasopressors (125), or other states of impaired microcirculation, edema, acidosis, dehydration, and extremes of glucose values (126–129).

The many variables that may reduce POC device reliability and accuracy (126) in the ICU have been reviewed in detail (4, 130) and the Food and Drug Administration (FDA) has defined limits of acceptable medication interference (126), but new therapeutic compounds may not be included. Clinicians are advised to understand the limitations of their specific devices and components of FDA 510(k) summaries. Further, a hierarchy of sampling procedures (site, methods, verification of out-of-range results, etc.) should be established and standardized to reduce between tester differences. Further, arterial or venous blood sources should be prioritized to mitigate the potential for factitious results with capillary testing and minimize trauma with repeated sampling. Availability of other analytic devices such as BG/blood gas analyzers (managed by laboratory or ICU personnel) could improve testing reliability but has similarly not been consistently tested.

Errors associated with POC devices are also applicable to subcutaneous CGM systems, and most devices are considered "off label" when used in the ICU (131). Guidance for hospital and ICU CGM use has been published (88, 132–134). Expanded utilization of CGM is expected with the "breakthrough device" waiver and expedited regulatory review (135). Observational reports during COVID-19 indicated feasibility in selected patients (136–138), although POC verification was suggested since inaccuracy was

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found. The pediatric experience similarly found inconsistent benefit in cardiac surgery patients for the identification of hypoglycemia (106). The manner of CGM implementation may be an important determinant of success and strategies have been proposed in a scoping review (139). Quantifying impact of CGM on workload will be an important endpoint.

Meanwhile, intravascular BG monitoring devices, which have also been prone to error, are not widely available (140). While artificial pancreas devices that combine CGMs, control algorithms, and insulin infusions may overcome many treatment and monitoring challenges, these are not broadly implemented or tested in the critically ill.

Important additional research issues for glucose monitoring devices include the subsets of patients most likely to benefit from their use, greater understanding of interfering substances, requirement for confirmatory BG testing, challenges around implementation, and documentation of results (e.g., need to capture all results in the EHR) and workload impact. A consensus statement has outlined analytical metrics for measurement of CGM use in hospitalized patients including endpoints of hypoglycemia, hyperglycemia, time in range, glycemic variability, device accuracy, and others (141). Feasibility of closed-loop insulin therapy is also a research opportunity.

ADDITIONAL TOPICS BEYOND THE SCOPE OF THIS GUIDELINE

There are many aspects of glycemic management that were not included due to the structure of the SCCM guideline process. Insulin is a high-risk medication and safe use requires a structured and consistent approach. Insulin safety and transitions of care that match patient acuity and route of administration were previously reviewed (4, 142) but remain important. Hypoglycemia is a serious risk and should be identified rapidly with processes designed for rapid patient rescue and immediate, protocolized treatment by nurses (5, 143, 144). The use of automated intelligence/machine learning may facilitate advanced warning of future dysglycemia events (145). Other topics not covered include combined nutritional titration with glycemic control interventions, perioperative management, and optimal metrics for hospital quality reporting.

CONCLUSIONS

Guidelines are limited by the quality of published data in RCTs and additional research topics have been proposed to close perceived gaps. Implementation of guidelines into clinical practice should consider current limitations in data and available local technology and expertise. Reevaluation of existing insulin protocols should be performed, relative to the recommendations within this guideline.

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